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(54) STORAGE-STABLE VITAMIN PREPARATIONS

(71) We, E. MERCK AKTIENGESellschaft, of 250 Frankfurter Strasse, Darmstadt, Germany, a Joint Stock Company organised under the laws of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with new, storage-stable vitamin compositions and with the preparation thereof.

It is known that a loss of content folic acid, panthothenyl alcohol and panthothenic acid and the salts thereof occurs in pharmaceutical compositions, especially in multi-vitamin compositions, during storage. Efforts to stabilise these vitamins with the help of galenical methods, for example, by the avoidance of concurrent granulation with other active materials, or by the addition of inert adjuvants, such as finely-divided silicic acid, have hitherto been unsuccessful.

We have now found that compositions containing these vitamins can be prepared with a most surprising galenical stability when at least one member selected from folic acid, panthothenyl alcohol, panthothenic acid and the salts of panthothenic acid are intimately mixed with galactomannans obtained from guar endosperm flour or carob bean seed flour. The addition of further stabilisers is hereby rendered unnecessary.

The new compositions according to the present invention additionally possess the considerable advantage that, in contradistinction to the previously known compositions, they can be ground without difficulty in conventional mills, such as pin mills and hammer mills. The powders thereby obtained are homogeneous, finely-divided and readily sievable. A further remarkable advantage of the new compositions is their outstanding solubility in cold and warm water so that a digestion or the liberation of the vitamins is ensured in all cases, not only in the case of physiological liberation in the body but also in the case of analytical investigations.

Consequently, according to one aspect of

the present invention, there is provided a process for the preparation of storage-stable, solid compositions containing at least one member selected from folic acid, panthothenyl alcohol, panthothenic acid and the salts of panthothenic acid, which consists in that at least one of these vitamins is intimately mixed with galactomannans obtained from guar endosperm flour or carob bean seed flour.

According to another aspect of the present invention, there are provided storage-stable, solid vitamin compositions comprising 0.1—50 parts by weight of at least one of the said vitamins intimately mixed with 99.9—50 parts by weight of galactomannans obtained from guar endosperm flour or carob bean seed flour.

The galactomannans are naturally-occurring hydrocolloids from the seeds of guar pods (*Cyamopsis tetragonoloba*) and from the seeds of the pods of the carob bean tree (*Ceratonia siliqua*). According to the chemical structure thereof, they are polysaccharides which consist of a long main chain of mannose molecules with single-membered side chains of galactose molecules. In the galactomannans obtained from guar endosperm flour, or a statistical average every second mannose unit bears a single-membered galactose side chain and in those obtained from carob bean seed flour, on average every fourth mannose unit bears a single-membered galactose side chain.

The galactomannans dissolve in water, possibly with warming. Even small concentrations can give highly viscous colloidal solutions.

The new compositions according to the present invention are prepared in the usual manner, preferably by evaporation of aqueous solutions which contain at least one of the said vitamins and the hydrocolloid. The evaporation to dryness expediently takes place under reduced pressure. The product obtained is comminuted, preferably by grinding, and possibly sieved. Of course, other drying processes can be used for the

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removal of the water, especially the conventional spray-drying processes.

The end product generally still contains 0.5—1.5% by weight of water. In accordance with requirements and intended use, the compositions according to the present invention contain 0.1—50 parts by weight of at least one of the vitamins selected from the group consisting of folic acid, pantothenyl alcohol, pantothenic acid and the salts of pantothenic acid and 99.9—50 parts by weight of galactomannans obtained from guar endosperm flour and/or carob bean seed flour. The multi-vitamin compositions according to the present invention preferably contain about 33.3 parts by weight of vitamin or vitamins and about 66.6 parts by weight of galactomannans.

The new compositions according to the present invention have a very good storage stability and, even in the case of storing for a comparatively long period of time, at different, even elevated temperatures, are more stable than compositions which have been prepared without the intimate mixing according to the present invention.

The compositions according to the present invention can, because of the physiological compatibility of the naturally-occurring hydrocolloids, be used not only as pharmaceuticals but also in the field of foodstuffs. Thus, they are suitable for use in pharmaceuticals or for the vitaminisation of foodstuffs and animal feeds and especially for the production of dielectric nutrients. In principle, the new compositions can be used wherever an addition of one or more of the said vitamins is desired.

The following Examples are given for the purpose of illustrating the present invention:

EXAMPLE 1.

Pantothenyl alcohol 3.33 kg.
Galactomannans ad 10.00 kg.

6.66 kg. of a galactomannan from guar endosperm flour or from carob bean seed flour are completely swollen up in about 100 litres water. To this solution is added the pantothenyl alcohol, diluted with water, and the mixture obtained is then dried by spraying into a spraying tower with an inlet temperature of 180°C. and an exit temperature of 80°C. The fine, spheroidal product obtained has a particle size of mainly 100 μ .

EXAMPLE 2.

Calcium pantothenate 0.33 kg.
Galactomannans ad 10.00 kg.

The galactomannan is swollen in 50 litres water, mixed with the calcium pantothenate, dissolved in water, and dried on trays in a vacuum drier at 40°C. The product obtained can be ground and reduced to any desired

particle size in any type of suitable mill, such as a pin mill or a hammer mill.

EXAMPLE 3.

Sodium pantothenate 0.033 kg. 65
Galactomannans ad 10.000 kg.

The intimate mixing is carried out in the manner described in Example 1 or 2.

EXAMPLE 4.

Folic acid 5.00 kg. 70
Galactomannans ad 10.00 kg.

The folic acid, in undissolved form, is stirred into the swollen galactomannans. The end product is obtained either by spraying or by vacuum drying. 75

EXAMPLE 5.

Pantothenyl alcohol/
galactomannans 33 $\frac{1}{3}$ % 21.0 mg.
potato starch 22.0 mg.
finely-divided silicic acid 13.0 mg. 80
cellulose powder 27.0 mg.
magnesium stearate 5.0 mg.
lactose ad 450.0 mg.

The pantothenyl alcohol/galactomannan composition is prepared in the manner described in Example 1. The individual components listed above are sieved and pressed into a tablet of 11 mm. diameter. Even after storage for several months, no loss of pantothenyl alcohol content can be detected. 90

EXAMPLE 6.

Thiamine phosphoric acid
ester phosphate salt 3.0 mg.
Calcium pantothenate/
galactomannans 33 $\frac{1}{3}$ % 15.0 mg. 95
Orotic acid 10.0 mg.
Tocopherol succinate 5.0 mg.
Pyridoxal hydrochloride 3.0 mg.
Folic acid/
galactomannans 50% 2.0 mg. 100
Riboflavin 3.0 mg.
Cyanocobalamine 5.0 γ
Maize starch 15.0 mg.
Lactose 15.0 mg.
Finely-divided silicic acid 3.0 mg. 105
Magnesium stearate ac 250.0 mg.

The calcium pantothenate/galactomannan composition is prepared in a manner analogous to that described in Example 2 and the folic acid/galactomannan composition in a manner analogous to that described in Example 4. The individual components listed above are sieved in the usual manner, mixed, granulated and pressed into tablets, each weighing 250.0 mg. and having a diameter 115 of 9 mm. Even after storage for several months, no loss of calcium pantothenate content can be detected.

EXAMPLE 7.

	Riboflavin	4.0 mg.
	Pyridoxal hydrochloride	4.0 mg.
	Thiamine mononitrate	5.0 mg.
5	Nicotinamide	15.0 mg.
	Pantothenyl alcohol/ galactomannan 33 $\frac{1}{3}$ %	9.9 mg.
	Orotic acid	25.0 mg.
	Tocopherol acetate	5.0 mg.
10	Finely-divided silicic acid	7.5 mg.
	Biotin	0.1 mg.
	Thioctic acid	5.0 mg.
	Cyanocobalamine	8.0 γ
	Magnesium stearate	2.5 mg.
15	Carboxymethyl cellulose	2.5 mg.
	Lactose	ad. 250.0 mg.

The pantothenyl alcohol/galactomannan composition is prepared in the manner described in Example 1. From the above-mentioned components, there is prepared a dragee core with the weight of 250 mg. and 9 mm. diameter. Cores prepared in this manner are then drageed in the usual manner with sugar, flour, titanium dioxide and talc to give dragees with a weight of 425 mg. The stability of the pantothenyl alcohol compositions was confirmed by storage experiments.

WHAT WE CLAIM IS:—

1. Storage-stable, solid vitamin compositions, comprising 0.1—50 parts by weight of at least one vitamin selected from folic acid, pantothenyl alcohol, pantothenic acid and the salts of pantothenic acid intimately mixed with 99.9—50 parts by weight of galactomannans obtained from guar endosperm flour and/or carob bean seed flour.

2. Compositions according to claim 1, which contain about 33.3 parts by weight of the vitamin or vitamins and about 66.6 parts by weight of the galactomannans.

3. Compositions according to claim 1, substantially as hereinbefore described and exemplified.

4. Process for the preparation of storage-stable, solid vitamin compositions, wherein 0.1—50 parts by weight of at least one vitamin selected from folic acid, pantothenyl alcohol, pantothenic acid and the salts of pantothenic acid are intimately mixed with 99.9—50 parts by weight of galactomannans obtained from guar endosperm flour and/or carob bean seed flour.

5. Process according to claim 4, wherein about 33.3 parts by weight of the vitamin or vitamins are intimately mixed with about 66.6 parts by weight of galactomannans.

6. Process according to claim 4 or 5, wherein the components are combined in water, with good mixing up, and the water subsequently removed.

7. Process according to claim 6, wherein the water is removed by evaporation under reduced pressure or by a spray drying process.

8. Process according to claim 4 for the preparation of storage-stable, solid vitamin compositions, substantially as hereinbefore described and exemplified.

9. Storage-stable, solid vitamin preparations, whenever prepared by the process according to any of claims 4—8.

10. Multivitamin compositions, whenever containing a composition according to any of claims 1—3 and 9.

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